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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,394	01/31/2001	Lars Wiklund	P/2432-37	5538

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Edward A Meilman
Dickstein Shapiro Morin & Oshinsky llp
1177 Avenue of the Americas 41st Floor
New York, NY 10036-2714

EXAMINER	
WANG, SHENGJUN	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,394	WIKLUND ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of applicants' amendments and remarks submitted April 18, 2006 is acknowledged.

Claim Rejections 35 U.S.C. 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 4-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites "pharmaceutical agents consisting essentially of (a) a first composition containing at least one of alpha-ketoglutarate and alpha—ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and be devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid." As currently amended, the claim further requires "wherein any composition administered containing at least one of alpha-ketoglutarate and alpha-ketoglutaric acid is devoid of ammonium." Claim 15 recites "pharmaceutical dosage unit comprising a first pharmaceutical composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and a second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and be devoid of a alpha-ketoglutarate and alpha-

ketoglutaric acid" Interpretated broadly, the claims read on separate compositions containing alpha-ketoglutarate and ammonium respectively. However, the application, as originally filed, lacks support for such separate composition. Particularly, the application provides no support for "composition containing at least one of alpha-ketoglutarate and alpha—ketoglutaric acid and ***being devoid*** of ammonium," "composition containing ammonium and ***being devoid*** of a alpha-ketoglutarate and alpha-ketoglutaric acid," "wherein any composition administered containing at least one of alpha-ketoglutarate and a-ketoglutaric acid is devoid of ammonium." in claim 1, and "pharmaceutical composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium," " pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and being devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid" in claim 15.

3. Further, claim 1 as currently amended, require "concomitant and ***separate***" administration. The application as originally filed lacks support for "***separate***" administration.

4. Furthermore, claim 15 recites "*pharmaceutical dosage unit comprising a first and second separate pharmaceutical compositions,* the first composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and a second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and be devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid" The application as originally filed provides no support for such pharmaceutical dosage unit.

5.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 4-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 recites "***concomitant and separate*** administration." The phrase is confusing in that how the administration is carried out concomitantly and separately. The specification or the claims provide no further clarification as the meaning of "concomitant and separate administration." The claim is indefinite as to how the administration is carried out.

Claim Rejections 35 U.S.C. 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Veech (USPN 5,719,119) and Vinnars (USPN 5,310,768), in further view of Taconic (http://www.taconic.com/anmodels/spragued.htm), and Bollish et al. (US 5,219,330).

The claims as currently amended, are directed to a dosage unit (a composition) comprising a first and second separate pharmaceutical composition, the first composition comprising at least one of alpha-ketoglutarate and alpha-ketoglutaric acid and being devoid of ammonium, and the second pharmaceutical composition comprising ammonium, and being

devoid of alpha-ketoglutarate and alpha-ketoglutaric acid; and method of concomitant and separate administration of this two composition. The administration herein claimed is construed as administering the two composition wherein the two compositions are separate before the administration, in view of the limitation "wherein any composition administered containing at least one of alpha-ketoglutarate and a-ketoglutaric acid is devoid of ammonium."

Veech (USPN 5,719,1 19) teaches a parenteral nutrition solution comprising carboxylic metabolite anions, such as lactate and/or alpha-Ketoglutarate, (0.1-150 mMole/L) and cation such as ammonium and sodium (0.1-150 mMole/L), See, particularly, columns 5. Particular examples comprising alpha-ketoglutarate and ammonium is disclosed. see Table 9, col.20, examples 1.4-1.5. Veech also teaches the employment of the parenteral nutrition solution comprising alpha-ketoglutarate in a method of normalizing muscle and organ function, see claims 5 and 6 for example. Veech further teaches that post-traumatic or post-operative patients suffer from a negative nitrogen balance, col.7, line 55 to column 8 line 7. Veech also teaches alpha ketoglutarate and ammonium in an amino acid solution containing glutamate which can control the redox state of the mitochondria and therefore be useful in nitrogen- containing pharmaceutical compositions, see col. 13 line 5 to col. 14 line 20. The parenteral composition is for intravenous administration. See, column 21, lines 1-8. Infusion rate of the composition to a Sprague Dawley male rate is about 2 ml/hour. It is noted Sprague Dawley male rat is normally less than 500 g in weight. See Prague Dawley Outbred rats (Taconic reference).

Vinnars (USPN 5,310,768) teaches a method of treatment of post operative and Post-traumatic patients for improving glutamine content in skeletal muscle and preventing the reduction of protein synthesis capacity, hence also, improve the nitrogen balance and even make

it positive by administering alpha-ketoglutarate, alone or in combination with other actives, see col. 2, lines 54-63 and abstract in particular. Vinnars teaches that the amount of alpha-ketoglutarate is at least 0.1g/kg body weight/day (which amounts to 312.5 micromoles/kg body weight per day), see col. 3, lines 6-12.

Veech and Vinnars do not particularly teach the dosing regimen herein in terms of micromoles per kilogram per minute, nor do they teach the administration of two separate compositions. Neither does it particularly teach the employment of a particular salt of ammonium.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to a dosage unit, wherein alpha-ketoglutarate and/or alpha-ketoglutaric acid, and ammonium are present separately in two composition, but are ready for the concomitant administration for preserving bodily protein, because both alpha-ketoglutarate and ammonium are known to be useful in methods of treating post-operative/post-traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. Concomitant administration of the two agents which are known to be useful to improve nitrogen balance and preserve skeletal muscle individually into a single composition useful for the very same purpose is prime facie obvious. See In re Kerkhoven 205 USPQ 1069. The employment of salts of known actives is within the skill of the Skilled Artisan and is therefore obvious. Furthermore, water, employed by Veech as the carrier, are both acceptable in parenteral composition and oral composition.

As to the particular concentration or dosing regimen herein, note it is well understood that optimization of effective amounts or and administrative regimens in pharmaceutical art is considered within the skill of the artisan. *Ex parte Skuballa* 12 USPQ2d 1570. Particularly, it is

noted that the particular regimens herein are well within the range disclosed by the prior art. For example, assume a composition comprising 100 mMole/L each of alpha-ketoglutarate and ammonium, is administered with a infusion rate of 30 mL/hour (or 0.5 mL/min) to a Patient with 50 kg, the rate would be 1 $\mu mol.kg^{-1}.min^{-1}$, well within the claimed range. It is well understood that "wherein the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F. 2d 454, 456, 105 USPQ 233,235 (CCPA 1955). Further, the optimization of a result effective parameter, e.g., effective amounts, is considered within the skill of the artisan. See, *In re Boesch and Slaney* (CCPA) 204 USPQ 215. Note normal operatable Intravenous infusion rate is in the range of 1 mL/hour to about 300 mL/hour in a duration of 1-24 hours. See, e.g., column 2, lines 55-68, column 5, lines 34-52 in Bollish et al. As to the limitation that requiring alpha-keto-glutarate and ammonium in separate compositions but with a dosage unit, the examiner contend that such dosage unit (and its concomitant administration) would have been obvious to a mixture of alph-glutarate and ammonium since such rearrangements provide no difference as to the therapeutical utility. One of ordinary skill in the art would have view such rearrangement as a obvious alternative of the mixture.

Response to the Arguments

Applicants' amendments and remarks submitted April 18, 2006 have been fully considered, but are not persuasive.

As to the written description rejections, applicants contend that the alleged new matters are supported by the disclosure at page 12, particularly the examples. The arguments are unconvincing. First, the disclosure never mentioned that ammonium composition is devoid of

alpha-keto-glutarate, nor glutarate composition is devoid of ammonium; second, the examples discloses experiments on piglets, the experiments begins with infusion of one compound last for 240 min, and start infusion of second compound 60 min after the start of the first compound. The disclosure never state eth second infusion is carried out in a *separate second* infusion line; third, the application never advances the experimental model in page 12 as the therapeutical method herein claimed which encompass human, and with further detailed requirements. Therefore, the application as originally filed does not support the new limitation recited in the claims.

As to the rejections under 35 U.S.C. 103, one of ordinary skill in the art would have view the concomitant administration of two agents as obvious alternative of administering the mixture of the two ingredients, absent evident to the contrary. Such rearrangement of the components without changing the utility is deemed to be obvious to one of ordinary skill in the art. See, In re Japikse, 181 F.2d 1019, 86 USPQ 70 (CCPA 1950); In re Kuhle, 526 F.2d 553, 188 USPQ 7 (CCPA 1975); In re Dulberg, 289 F.2d 522, 523, 129 USPQ 348, 349 (CCPA 1961). Further, even assume the claimed invention require the second infusion, such limitation would not make the claimed invention patentably distinct from the prior art. The prior art teach the infusion of the mixture of the two ingredients. The infusion of the two ingredients separate but concomitant in two infusion is indeed different form the prior art, but not in a patentable distinct way. The application provides no evidence that the separate infusions are actually better than the single infusion in the aspect of therapeutic efficacy. Obviously, the separate infusion is a bit of inconvenience compared to the single infusion. However, this inconvenience would not make it patentable distinct. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the

same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132.

As to the increase of infusion of ammonium, it is noted that the art permit a large range as to the infusion rate, therefore, the variation of infusion rate within the art recognized range is within the purview of the artisan, absent evidence to the contrary.

No claim is allowable.

With respect to the duration of administration a therapeutic agent, infusion rate, the examiner recognizes the optimization of a result effective parameter, e.g., effective amounts or therapeutic regimen of a pharmaceutical agent, is considered within the skill of the artisan. See, *In re Boesch and Slaney* (CCPA) 204 USPQ 215.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER

Shengjun Wang
Primary Examiner
Art Unit 1617